

## REVISITING REML IN MIXED EFFECTS MODELS: A NON-ITERATIVE PROCEDURE

**Raffaella Artusi, Ettore Marubini**

*Medical Statistics and Biometry Unit, Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan, Italy (E.M., R.A.); Institute of Medical Statistics and Biometry, University of Milan, Milan, Italy (E.M.).*

### ABSTRACT

*It is well known that in mixed effects models the restricted maximum likelihood estimation procedure makes it possible to obtain unbiased estimates of variance components and fixed effects. In this paper, such a procedure is thoroughly described, enlightening that no iterative process is necessary involved, thereby avoiding all convergence problem. Nevertheless, in this way more than one solution for the estimates of the unknown variance parameters can be obtained. Thus, how to choose among the possible different solutions is suggested.*

**KEY WORDS:** *Unbalanced factorial design; symbolic computation.*

### 1. INTRODUCTION

The use of mixed models is becoming more and more popular to analyze clinical as well as epidemiological data. Several papers have been published on the topic, as, recently, by Brown and Prescott (1999) and Verbeke and Molenberghs (2000) respectively. Among the estimation procedures, the restricted maximum likelihood (REML) method is discussed, and the results of pertinent computations are illustrated by resorting to computer packages currently used in statistical laboratories. All of these are based on an iterative estimation procedure, the history of which can be properly evaluated by ad hoc tables like, for instance, the one printed by SAS PROC MIXED. However, from a didactic viewpoint, such an approach appears to be questionable, as the reader, not being involved in each of the steps of the estimation process, risks not grasping the rationale of the process itself. Alternatively, an estimation approach accomplished by means of a computer package for symbolic computation, such as MAPLE V (1991), can avoid this drawback as the user has to follow the estimation process step by step.

In the present paper, attention is focused on the REML method of estimation of variance components and fixed effects of a linear mixed effects model with a quantitative continuous response. Thus, Section 2 introduces the underlying regression model, and the REML estimation method is given in detail. Concluding remarks are given in Section 3.

## 2. REML ESTIMATION METHOD OF VARIANCE COMPONENTS AND FIXED EFFECTS

It is known that in the fixed effects model, the residual error sums up the effects of all undefined sources of variability, whereas in the mixed effects model one or more sources of random variation are made explicit. A linear mixed effects model is usually defined as (Corbeil and Searle, 1976):

$$\mathbf{y} = \mathbf{X}\boldsymbol{\alpha} + \mathbf{U}_1\boldsymbol{\beta}_1 + \mathbf{U}_2\boldsymbol{\beta}_2 + \cdots + \mathbf{U}_c\boldsymbol{\beta}_c + \boldsymbol{\varepsilon} \quad (1)$$

where:  $\mathbf{y}$  = vector of  $N$  empirical realizations of a random variable  $Y$ ;  $\mathbf{X}$  = fixed effects  $(N, k)$  design matrix of rank  $k$ ;  $\boldsymbol{\alpha}$  = vector of the fixed effect parameters;  $\mathbf{U}_i = (N, k_i)$  design matrix for the  $i$ th random effect ( $i = 1, 2, \dots, c$ );  $\boldsymbol{\beta}_i$  = vector of parameters for the  $\mathbf{U}_i$  matrix;  $\boldsymbol{\varepsilon}$  = vector of residuals.

The vectors  $\boldsymbol{\beta}_i$  are assumed to be i.i.d.  $N(0, \sigma_i^2)$  and  $\boldsymbol{\varepsilon}$  i.i.d.  $N(0, \sigma_\varepsilon^2)$ ; as a consequence,  $\mathbf{y} \sim N(\mathbf{X}\boldsymbol{\alpha}, \mathbf{V})$ , where the variance-covariance matrix  $\mathbf{V}$  can be written as  $\sigma_\varepsilon^2 \mathbf{H}$ , with  $\mathbf{H}$  as follows:

$$\mathbf{H} = \sum_{i=1}^c \gamma_i \mathbf{U}_i \mathbf{U}_i' + \mathbf{I}_N \quad (2)$$

with  $\gamma_i = \frac{\sigma_i^2}{\sigma_\varepsilon^2}$ .

The likelihood of  $\mathbf{y}$  is:

$$L(\mathbf{y}) = \frac{1}{\sqrt{(2\pi)^N |\mathbf{V}|}} \exp \left\{ -\frac{1}{2} (\mathbf{y} - \mathbf{X}\boldsymbol{\alpha})' \mathbf{V}^{-1} (\mathbf{y} - \mathbf{X}\boldsymbol{\alpha}) \right\} \quad (3)$$

It is known that the variance component estimates attained by maximizing this likelihood are biased. This drawback can be avoided by means of the REML method as it enables a proper partition of the degrees of freedom. The latter consists in separating random from fixed effects through a transformation of  $\mathbf{y}$  into a vector  $\mathbf{z}$ :

$$\mathbf{z} = \begin{bmatrix} \mathbf{T} \\ \mathbf{Q} \end{bmatrix} \mathbf{y} = \begin{bmatrix} \mathbf{z}_1 \\ \mathbf{z}_2 \end{bmatrix} \sim N \left( \begin{bmatrix} \mathbf{0} \\ \mathbf{X}\boldsymbol{\alpha} \end{bmatrix}, \begin{bmatrix} \mathbf{THT}'\sigma_\varepsilon^2 & \mathbf{0} \\ \mathbf{0} & \mathbf{QHQ}'\sigma_\varepsilon^2 \end{bmatrix} \right)$$

Vectors  $\mathbf{y}$  and  $\mathbf{z}$  must belong to the same  $N$ -dimensional space; however,  $\mathbf{z}$  can be separated into two stochastically independent vectors  $\mathbf{z}_1$  and  $\mathbf{z}_2$  of dimension  $N-k$  and  $k$ , respectively. The former vector, independent of fixed effects, accounts for the random components, whereas the second vector, independent of random components, accounts for the fixed effects. This allows splitting the likelihood of  $\mathbf{z}$  into two independent parts ( $L(\mathbf{z}) = L(\mathbf{z}_1) \cdot L(\mathbf{z}_2)$ ) and estimating variance components, random and fixed effects separately.

Since the linear model:

$$\mathbf{y} = \mathbf{X}\boldsymbol{\alpha} + \boldsymbol{\varepsilon}$$

where  $\mathbf{y} \sim N(\mathbf{X}\boldsymbol{\alpha}, \mathbf{V} = \sigma_\varepsilon^2 \mathbf{I})$ , represents the simplest form of model (1), obtaining the transformation of  $\mathbf{y}$  in this context can suggest an overall way to find the transformation matrices  $\mathbf{T}$  and  $\mathbf{Q}$ . In the simplest case, one can consider the projections of the observation vector  $\mathbf{y}$  into the two orthogonal spaces spanned by the linearly independent column of the matrices  $\mathbf{P} = \mathbf{X}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}'$  and  $\mathbf{S} = (\mathbf{I} - \mathbf{P})$ .

Since the rank of  $\mathbf{X}$ ,  $\mathbf{X}'\mathbf{X}$  and  $(\mathbf{X}'\mathbf{X})^{-1}$  is  $k$ , it follows that  $\mathbf{P}$  and  $\mathbf{S}$  have rank  $k$  and  $N - k$ , respectively, so that  $\mathbf{P}$  projects the vector  $\mathbf{y}$  from an  $N$ -dimensional space  $\Omega$  into a  $k$ -dimensional subspace  $\Omega_1$  (*space of fitted values*), whereas  $\mathbf{S}$  projects  $\mathbf{y}$  into an  $(N-k)$ -dimensional subspace  $\Omega_2$  (*space of residual errors*).

Thus, the two  $N$ -dimensional projection vectors of  $\mathbf{y}$  are defined as:

$$\mathbf{z}_1 = \mathbf{S}\mathbf{y} = (\mathbf{I} - \mathbf{X}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}')\mathbf{y} = \mathbf{I}\mathbf{y} - \mathbf{X}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}'\mathbf{y} = \mathbf{y} - \mathbf{X}\hat{\boldsymbol{\alpha}} = \boldsymbol{\varepsilon}$$

$$\mathbf{z}_2 = \mathbf{P}\mathbf{y} = \mathbf{X}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}'\mathbf{y} = \mathbf{X}\hat{\boldsymbol{\alpha}}$$

where  $\mathbf{z}_1 \sim N(0, \sigma_\varepsilon^2)$  and  $\mathbf{z}_2 \sim N(\mathbf{X}\boldsymbol{\alpha}, \mathbf{P}\sigma_\varepsilon^2)$ . Since

$$\begin{aligned} \text{Cov}(\mathbf{z}_1, \mathbf{z}_2) &= \text{Cov}(\mathbf{P}\mathbf{y}, \mathbf{S}\mathbf{y}) = \text{Cov}(\mathbf{P}\mathbf{y}, (\mathbf{I} - \mathbf{P})\mathbf{y}) = \\ &= \mathbf{P}\mathbf{V}(\mathbf{I} - \mathbf{P})' = \mathbf{P}(\mathbf{I}\sigma_\varepsilon^2)(\mathbf{I} - \mathbf{P}) = \mathbf{0} \end{aligned}$$

$\mathbf{z}_1$  and  $\mathbf{z}_2$  are orthogonal.

As the rank of  $\mathbf{S}$  is  $N - k$ , one can obtain a matrix  $\mathbf{T}$  of the same rank by deleting  $k$  linearly dependent rows of  $\mathbf{S}$  and, analogously, being  $k$  the rank of  $\mathbf{P}$ , one can obtain a matrix  $\mathbf{Q}$  of the same rank by deleting  $N - k$  linearly dependent rows of  $\mathbf{P}$ . The matrices  $\mathbf{Q}$  and  $\mathbf{T}$  allow defining

$$\mathbf{z} = \begin{bmatrix} \mathbf{T} \\ \mathbf{Q} \end{bmatrix} \mathbf{y} = \begin{bmatrix} \mathbf{z}_1 \\ \mathbf{z}_2 \end{bmatrix} \sim N \left( \begin{bmatrix} \mathbf{0} \\ \mathbf{X}^* \boldsymbol{\alpha} \end{bmatrix}, \begin{bmatrix} \mathbf{T} \mathbf{T}' \sigma_\varepsilon^2 & \mathbf{0} \\ \mathbf{0} & \mathbf{Q} \mathbf{Q}' \sigma_\varepsilon^2 \end{bmatrix} \right)$$

where  $\mathbf{z}_1$  and  $\mathbf{z}_2$  are stochastically independent vectors of  $N - k$  and  $k$  dimension, respectively. Furthermore, note that  $\mathbf{X}^*$  is the matrix derived from  $\mathbf{X}$  by deleting the same rows deleted from  $\mathbf{P}$  to get  $\mathbf{Q}$ .

$L(\mathbf{z})$  can now be written as the product of:

$$L(\mathbf{z}_1) = \frac{1}{\sqrt{(2\sigma_\varepsilon^2)^{N-k} |\mathbf{T} \mathbf{T}'|}} \exp \left\{ -\frac{1}{2\sigma_\varepsilon^2} (\mathbf{T} \mathbf{y})' (\mathbf{T} \mathbf{T}')^{-1} (\mathbf{T} \mathbf{y}) \right\} \quad (4)$$

and

$$L(\mathbf{z}_2) = \frac{1}{\sqrt{(2\pi\sigma_\varepsilon^2)^k |\mathbf{Q} \mathbf{Q}'|}} \exp \left\{ -\frac{1}{2\sigma_\varepsilon^2} (\mathbf{Q} \mathbf{y} - \mathbf{X}^* \boldsymbol{\alpha})' (\mathbf{Q} \mathbf{Q}')^{-1} (\mathbf{Q} \mathbf{y} - \mathbf{X}^* \boldsymbol{\alpha}) \right\} \quad (5)$$

where  $L(\mathbf{z}_1)$  depends only on the residual vector  $\boldsymbol{\varepsilon}$ , whereas  $L(\mathbf{z}_2)$  depends only on fixed effects.

Going back to the mixed effects model, one realizes that being  $\mathbf{V} = \sigma_\varepsilon^2 \mathbf{H}$ :

$$\text{Cov}(\mathbf{P} \mathbf{y}, (\mathbf{I} - \mathbf{P}) \mathbf{y}) = \mathbf{P} \mathbf{V} (\mathbf{I} - \mathbf{P})' = \mathbf{P} (\mathbf{H} \sigma_\varepsilon^2) (\mathbf{I} - \mathbf{P}) \neq \mathbf{0}$$

This does not allow partitioning the likelihood of  $\mathbf{z}$  in two parts enabling estimating variance components, random and fixed effects separately. To this purpose, a different definition of the matrix  $\mathbf{Q}$  is needed. Let  $\mathbf{Q}$  be the unknown transformation matrix of  $\mathbf{y}$  such that  $\mathbf{S}$  and  $\mathbf{Q}$  are orthogonal with respect to  $\mathbf{V} = \sigma_\varepsilon^2 \mathbf{H}$ :

$$\text{Cov}(\mathbf{S} \mathbf{y}, \mathbf{Q} \mathbf{y}) = \mathbf{S} \mathbf{V} \mathbf{Q}' = \mathbf{S} \mathbf{H} \mathbf{Q}' \sigma_\varepsilon^2 = \mathbf{0}$$

As  $\sigma_\varepsilon^2$  is positive,  $\mathbf{S} \mathbf{H} \mathbf{Q}'$  must be equal to the null matrix. Since  $\mathbf{S} \mathbf{X} = (\mathbf{I} - \mathbf{P}) \mathbf{X} = \mathbf{0}$ , one can write  $\mathbf{S} \mathbf{H} \mathbf{Q}' = \mathbf{S} \mathbf{X}$ . Therefore the easiest choice for  $\mathbf{Q}$  is  $\mathbf{H} \mathbf{Q}' = \mathbf{X}$ , and consequently  $\mathbf{Q} = \mathbf{X}' \mathbf{H}^{-1}$ . It is note worthy that  $\mathbf{X}' \mathbf{H}^{-1}$  is a  $(k, N)$  matrix of rank  $k$ . As a consequence, if  $\mathbf{Q} = \mathbf{X}' \mathbf{H}^{-1}$  and  $\mathbf{T}$  is obtained by deleting  $k$  dependent rows of  $\mathbf{S}$ , an  $N$ -dimensional vector  $\mathbf{z}$  can be defined as:

$$\mathbf{z} = \begin{bmatrix} \mathbf{T} \\ \mathbf{Q} \end{bmatrix} \mathbf{y} = \begin{bmatrix} \mathbf{T} \\ \mathbf{X}' \mathbf{H}^{-1} \end{bmatrix} \mathbf{y} = \begin{bmatrix} \mathbf{T} \mathbf{y} \\ \mathbf{X}' \mathbf{H}^{-1} \mathbf{y} \end{bmatrix} = \begin{bmatrix} \mathbf{z}_1 \\ \mathbf{z}_2 \end{bmatrix}$$

$$\begin{bmatrix} \mathbf{z}_1 \\ \mathbf{z}_2 \end{bmatrix} \sim N \left( \begin{bmatrix} \mathbf{0} \\ \mathbf{X}' \mathbf{H}^{-1} \mathbf{X} \boldsymbol{\alpha} \end{bmatrix}, \begin{bmatrix} \mathbf{T} \mathbf{H} \mathbf{T}' \sigma_\varepsilon^2 & \mathbf{0} \\ \mathbf{0} & \mathbf{X}' \mathbf{H}^{-1} \mathbf{X} \sigma_\varepsilon^2 \end{bmatrix} \right)$$

Then, analogously to (4) and (5), the likelihood  $L(\mathbf{z})$  can be written as the product of  $L(\mathbf{z}_1)$  and  $L(\mathbf{z}_2)$ :

$$L(\mathbf{z}_1) = \frac{1}{\sqrt{(2\pi\sigma_\varepsilon^2)^{N-k} |\mathbf{THT}'|}} \exp\left\{-\frac{1}{2\sigma_\varepsilon^2} (\mathbf{T}\mathbf{y})' (\mathbf{THT}')^{-1} (\mathbf{T}\mathbf{y})\right\}$$

$$L(\mathbf{z}_2) = \frac{1}{\sqrt{(2\pi\sigma_\varepsilon^2)^k |\mathbf{X}'\mathbf{H}^{-1}\mathbf{X}|}} \exp\left\{-\frac{1}{2\sigma_\varepsilon^2} (\mathbf{X}'\mathbf{H}^{-1}\mathbf{y} - \mathbf{X}'\mathbf{H}^{-1}\mathbf{X}\boldsymbol{\alpha})' (\mathbf{X}'\mathbf{H}^{-1}\mathbf{X})^{-1} (\mathbf{X}'\mathbf{H}^{-1}\mathbf{y} - \mathbf{X}'\mathbf{H}^{-1}\mathbf{X}\boldsymbol{\alpha})\right\}$$

$$= \frac{1}{\sqrt{(2\pi\sigma_\varepsilon^2)^k |\mathbf{X}'\mathbf{H}^{-1}\mathbf{X}|}} \exp\left\{-\frac{1}{2\sigma_\varepsilon^2} (\mathbf{y} - \mathbf{X}\boldsymbol{\alpha})' \mathbf{H}^{-1}\mathbf{X} (\mathbf{X}'\mathbf{H}^{-1}\mathbf{X})^{-1} \mathbf{X}'\mathbf{H}^{-1} (\mathbf{y} - \mathbf{X}\boldsymbol{\alpha})\right\}$$

As in (4) and (5),  $L(\mathbf{z}_1)$  depends only on random effects, whereas  $L(\mathbf{z}_2)$  depends only on fixed effects.  $L(\mathbf{z}_1)$  enables one to obtain the REML estimates of variance components  $\hat{\sigma}_\varepsilon^2$  and  $\hat{\gamma}_i$ .

More conveniently, the latter are obtained by deriving the logarithm of  $L(\mathbf{z}_1)$  with respect to  $\sigma_\varepsilon^2$  and  $\gamma_i$ , for each  $i$ .

$$l(\mathbf{z}_1) \propto -\frac{1}{2}(N-k) \log \sigma_\varepsilon^2 - \frac{1}{2} \log |\mathbf{THT}'| - \frac{1}{2\sigma_\varepsilon^2} (\mathbf{T}\mathbf{y})' (\mathbf{THT}')^{-1} (\mathbf{T}\mathbf{y}) \quad (6)$$

While  $\sigma_\varepsilon^2$  is explicitly given in (6), the matrix  $\mathbf{H}$ , as defined in (2), makes  $l(\mathbf{z}_1)$  a function of the  $\gamma_i$ 's.

Recalling (Basilevsky, 1983) that:

$$\frac{\partial \log |\mathbf{AXB}|}{\partial \mathbf{X}} = |\mathbf{AXB}| \mathbf{A}' [(\mathbf{AXB})^{-1}] \mathbf{B}'$$

$$\frac{\partial |\mathbf{AXB}|}{\partial \mathbf{X}} = \mathbf{A}' [(\mathbf{AXB})^{-1}] \mathbf{B}'$$

where  $\mathbf{A}$ ,  $\mathbf{B}$ ,  $\mathbf{X}$  are not singular, the derivatives of  $l(\mathbf{z}_1)$  are:

$$\frac{\partial l(\mathbf{z}_1)}{\partial \sigma_\varepsilon^2} = -\frac{1}{2\sigma_\varepsilon^2} (N-k) + \frac{1}{2\sigma_\varepsilon^4} \mathbf{y}' \mathbf{T}' (\mathbf{THT}')^{-1} \mathbf{T}\mathbf{y} \quad (7)$$

$$\frac{\partial l(\mathbf{z}_1)}{\partial \gamma_i} = -\frac{1}{2} \mathbf{U}_i' \mathbf{T}' (\mathbf{THT}')^{-1} \mathbf{T}\mathbf{U}_i + \frac{1}{2\sigma_\varepsilon^2} \mathbf{U}_i' \mathbf{T}' (\mathbf{THT}')^{-1} \mathbf{T}\mathbf{y} \mathbf{y}' \mathbf{T}' (\mathbf{THT}')^{-1} \mathbf{T}\mathbf{U}_i \quad (8)$$

for each  $i=1,2,\dots,c$ .

Each derivative must be equalized to zero in a system of equations:

$$\begin{cases} -\frac{1}{2\sigma_\varepsilon^2}(N-k) + \frac{1}{2\sigma_\varepsilon^4} \mathbf{y}' \mathbf{T}' (\mathbf{THT}')^{-1} \mathbf{T} \mathbf{y} = 0 & (9) \\ \frac{1}{2} \mathbf{U}_i' \mathbf{T}' (\mathbf{THT}')^{-1} \mathbf{T} \mathbf{U}_i = \frac{1}{2\sigma_\varepsilon^2} \mathbf{U}_i' \mathbf{T}' (\mathbf{THT}')^{-1} \mathbf{T} \mathbf{y} \mathbf{y}' \mathbf{T}' (\mathbf{THT}')^{-1} \mathbf{T} \mathbf{U}_i \quad \text{for } i=1,2,\dots,c & (10) \end{cases}$$

As  $\frac{\partial l(\mathbf{z}_1)}{\partial \gamma_i}$  is a  $(k_i, k_i)$  matrix, (10) represents  $k_i$  equations, but only one equation is needed for each  $i$ . It is known that if  $\mathbf{A} = \mathbf{B}$  then  $\text{trace}(\mathbf{A}) = \text{trace}(\mathbf{B})$ . Thus applying to (10) the invariant transformation given by the trace of the matrix, the system becomes:

$$\begin{cases} \hat{\sigma}_\varepsilon^2 = \frac{1}{N-k} \mathbf{y}' \mathbf{T}' (\mathbf{THT}')^{-1} \mathbf{T} \mathbf{y} \\ \text{trace}(\mathbf{U}_i' \mathbf{T}' (\mathbf{THT}')^{-1} \mathbf{T} \mathbf{U}_i) = \frac{1}{\hat{\sigma}_\varepsilon^2} \mathbf{y}' \mathbf{T}' (\mathbf{THT}')^{-1} \mathbf{T} \mathbf{U}_i \mathbf{U}_i' \mathbf{T}' (\mathbf{THT}')^{-1} \mathbf{T} \mathbf{y} \quad \text{for } i=1,2,\dots,c & (11) \end{cases}$$

The estimates of  $\sigma_\varepsilon^2$  and  $\gamma_i$  can be obtained by solving the previous system of equations.

After substituting these estimates in  $\mathbf{H}$  and, consequently, in  $L(\mathbf{z}_2)$ , fixed effects estimates can be attained by deriving  $l(\mathbf{z}_2)$ , the logarithm of  $L(\mathbf{z}_2)$ , with respect to  $\boldsymbol{\alpha}$  and equaling this derivative to zero:

$$l(\mathbf{z}_2) = -\frac{1}{2} \log(2\pi\hat{\sigma}_\varepsilon^2)^k |\mathbf{X}' \hat{\mathbf{H}}^{-1} \mathbf{X}| - \frac{1}{2\hat{\sigma}_\varepsilon^2} (\mathbf{y} - \mathbf{X}\boldsymbol{\alpha})' \hat{\mathbf{H}}^{-1} \mathbf{X} (\mathbf{X}' \hat{\mathbf{H}}^{-1} \mathbf{X})^{-1} \mathbf{X}' \hat{\mathbf{H}}^{-1} (\mathbf{y} - \mathbf{X}\boldsymbol{\alpha})$$

$$\frac{\partial l(\mathbf{z}_2)}{\partial \boldsymbol{\alpha}} = \frac{1}{\hat{\sigma}_\varepsilon^2} \mathbf{X}' \hat{\mathbf{H}}^{-1} \mathbf{X} (\mathbf{X}' \hat{\mathbf{H}}^{-1} \mathbf{X})^{-1} \mathbf{X}' \hat{\mathbf{H}}^{-1} (\mathbf{y} - \mathbf{X}\boldsymbol{\alpha}) = \frac{1}{\hat{\sigma}_\varepsilon^2} \mathbf{X}' \hat{\mathbf{H}}^{-1} (\mathbf{y} - \mathbf{X}\boldsymbol{\alpha})$$

$$\frac{1}{\hat{\sigma}_\varepsilon^2} \mathbf{X}' \hat{\mathbf{H}}^{-1} (\mathbf{y} - \mathbf{X}\boldsymbol{\alpha}) = \mathbf{0}$$

Then the solution is:

$$\hat{\boldsymbol{\alpha}} = (\mathbf{X}' \hat{\mathbf{H}}^{-1} \mathbf{X})^{-1} \mathbf{X}' \hat{\mathbf{H}}^{-1} \mathbf{y} \quad (12)$$

whose variance is:

$$\text{Var}(\hat{\boldsymbol{\alpha}}) = (\mathbf{X}' \hat{\mathbf{H}}^{-1} \mathbf{X})^{-1} \mathbf{X}' \hat{\mathbf{H}}^{-1} \text{Var}(\mathbf{y}) \hat{\mathbf{H}}^{-1} \mathbf{X} (\mathbf{X}' \hat{\mathbf{H}}^{-1} \mathbf{X})^{-1} =$$

$$\begin{aligned}
 &= (\mathbf{X}' \hat{\mathbf{H}}^{-1} \mathbf{X})^{-1} \mathbf{X}' \hat{\mathbf{H}}^{-1} \hat{\mathbf{H}} \hat{\mathbf{H}}^{-1} \mathbf{X} (\mathbf{X}' \hat{\mathbf{H}}^{-1} \mathbf{X})^{-1} = \\
 &= (\mathbf{X}' \hat{\mathbf{H}}^{-1} \mathbf{X})^{-1}
 \end{aligned}$$

The vector  $\hat{\boldsymbol{\alpha}}$  is the same one can obtain by deriving  $L(\mathbf{y})$ , i.e. maximum likelihood, or using the generalized least-squares method.

Finally, random effects estimates can be obtained by applying empirical Bayesian techniques.

A MapleV file, reporting instructions for no-iterative estimating of variance components and fixed effects through the REML procedure applied to data emerging from a  $3 \times 2$  unbalanced factorial design (Hemmerle and Hartley, 1976), is available at <http://xxx/xxx><sup>1</sup>.

### 3. CONCLUDING REMARKS

Equations (9) and (11) are usually not linear in the unknown variance parameters ( $\gamma_i$  and  $\sigma_\epsilon^2$ ), which implies that more than one solution may be found. In this case the solution that should be chosen is the one, generally unique, having the smallest and all positive estimates of the variance parameters. When this is not possible, probably an overparametrised model has been chosen; then, to find the latent variables not to be used, we propose the following steps:

- i) to estimate  $\sigma_\epsilon^2$  by assuming a fixed effects model for all the effects;
- ii) to run the mixed effects model and, among the solutions gathered, choose the one having  $\hat{\sigma}_\epsilon^2$  nearest to the corresponding estimate in i);
- iii) if the solution in ii) includes negative estimates for one or more  $\gamma_i$ , to equate them to zero;
- iv) to delete the equations corresponding to the derivatives of restricted likelihood with respect to those of  $\gamma_i$ ;
- v) to find new solutions to the reduced system of equations.

Resorting to computer packages for symbolic computation, like MapleV, allows highlighting that no iterative process is involved, and thereby all convergence problems are avoided.

---

<sup>1</sup> Manca l'indirizzo internet.

## REFERENCES

- BASILEVSKY A., 1983, *Applied Matrix Algebra in the Statistical Sciences*, New York: North-Holland.
- BROWN H., and PRESCOTT R., 1998, *Applied Mixed Models in Medicine*, Chichester: John Wiley & sons, Inc.
- CORBEIL R.R., and SEARLE S.R., 1976, Restricted Maximum Likelihood (REML) Estimation of Variance Components in the Mixed Model, *Technometrics*, 18, 31 - 38.
- HEMMERLE W. J., and HARTLEY H. O., 1973, Computing Maximum Likelihood Estimates for the Mixed A.O.V. Model Using the W Transformation, *Technometrics*, 15, 819 - 831.
- MILLIKEN G. A., and JOHNSON D. E., 1984, *Analysis of Messy Data* (vol.1), New York: Van Nostrand Reinhold Company.
- SEARLE S. R., CASELLA G., MCCULLOCH C. E., 1992, *Variance Components*, New York: John Wiley & sons, Inc..
- VERBEKE G., and MOLENBERGHS G., 2000, *Linear Mixed Models for Longitudinal Data*, New York: Springer.

## RIVISITAZIONE DEL METODO DI STIMA BASATO SULLA VEROSIMIGLIANZA RISTRETTA (REML) NEI MODELLI A EFFETTI MISTI: UNA PROCEDURA NON ITERATIVA

### *Riassunto*

*È noto che, nei modelli ad effetti misti, la procedura di stima basata sulla massimizzazione della verosimiglianza ristretta consente di ottenere stime non distorte sia delle componenti di varianza sia degli effetti fissi. In questo articolo tale procedura è descritta nel dettaglio, mettendo in luce come non sia necessario applicare alcun processo di stima iterativo, evitando così ogni problema di convergenza. Tuttavia in questo modo si può ottenere più di una soluzione come stima dei parametri di varianza. Viene allora suggerito come scegliere tra le varie soluzioni.*